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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,804	03/22/2004	David C. Baulcombe	101044.53943D2	9959

110 7590 10/21/2005

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1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
MEHTA, ASHWIN D	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,804	BAULCOMBE ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-110* is/are pending in the application.

4a) Of the above claim(s) *45-59,81,82 and 84-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-44,60-80,83 and 93-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/491,549.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6302004; 2162005;* 8222005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 33-39, 60-65, 69-83, 100, and 101, and the species election of plants, in the reply filed on July 21, 2005 is acknowledged. The traversal is on the ground(s) that MPEP 803 allegedly indicates two criteria must be satisfied to warrant restriction: 1) that the inventions be independent and distinct and 2) there must be a serious search burden. Applicants argue that Groups I, II, and IV are drawn to similar subject matter and are not independent and distinct (response, page 16, 1st full paragraph to the paragraph bridging pages 16-17). However, the MPEP 803 indicates that the first criterion is independent *or* distinct, not independent and distinct (emphasis added). The restriction requirement mailed July 7, 2005 did provide reasons why the groups are patentably distinct. Applicants also argue that a search of Groups I, II, and IV require searching for methods of inducing PTGS using any recombinant nucleic acid methodology and such a search would encompass RNA and DNA molecules (response, page 16, 1st full paragraph). Upon further consideration, examination of claims 40-44, 66-68, 99, and 103 together with the claims of Group I was not deemed to impose an additional serious burden, and those two groups have been rejoined. However, the methods of Group IV require steps that are not required for Group I, and which would require further searching and consideration. Searching methodologies that are not required for a claimed elected invention imposes an undue burden. Applicants also traverse the election of species requirement, arguing that PTGS has been observed in species as diverse as humans, plants, nematodes and fungi, and is always correlated with the presence of SRMs

(response, paragraph bridging pages 17-18). However, methods of introducing nucleic acids into one specie of organism is not the same for all other species. Searching and examination of such methods for all organisms encompassed by the claims do impose an undue burden.

The requirement regarding Groups III and IV is still deemed proper and is therefore made FINAL. Claims 33-44, 60-83, and 93-110 and the species of plants have been examined in this Office action.

Priority

2. The statement of priority on page 1 of the specification should be amended to recite the status (allowed or abandoned) of the parent U.S. application. If it was allowed, the U.S. patent number should be inserted.

3. The preliminary amendment filed March 22, 2004, inserting a claim of priority to U.S. application number 09/491,549 and GB9925459.1 is objected because it indicates that each of these applications are incorporated by reference. This is new matter, because the oath/declaration does not refer to the preliminary amendments. For the incorporation by reference to be effective as a proper safeguard against the omission of a portion of a prior application, the incorporation by reference statement must be included in the specification-as-filed, or transmittal letter-as-filed, or in an amendment specifically referred to in an oath or declaration executing the application. An incorporation by reference statement added after an application's filing date is not effective because no new matter can be added to an application after its filing date (see 35 U.S.C. 132(a)). For the incorporation by reference to be effective as a

proper safeguard, the incorporation by reference statement must be filed at the time of filing of the later-filed application. An incorporation by reference statement added after an application's filing date is not effective because no new matter can be added to an application after its filing date (see 35 U.S.C. 132(a)). Note that changes to the rules governing incorporation by reference that became effective on September 21, 2004 apply to applications filed on or after September 21, 2004.

Information Disclosure Statement

4. In the IDS filed June 30, 2004, Applicants included two Notice of References Cited pages that were filed by the examiner of parent application 09/491,549. The references have been considered in the instant application. However, the citations were not initialed by the examiner because they did not appear on a form 1449. It is suggested that Applicants submit a supplemental IDS that lists these references on a form 1449.

Abstract

5. The abstract of the disclosure is objected to because it is too long and does not refer to the claimed, examined invention. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said,"

should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

6. Claims 75, 77, 97, 102, and 108 are objected to for the following reasons:

Claims 75, 77, 97, and 108 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 75 attempts to limit the method of claim 71 by indicating that the "target gene is expressed by a virus, parasite, or predator of an organism containing said target gene". It is unclear from this recitation if the target gene is located in the virus, parasite, or predator, or the organism (See the indefinite rejection below. The organism is considered to be a plant, as that is the elected species). Claim 71 indicates that the SRM silences a target gene in the cell into which it was introduced. If the target gene in claim 75 is in a virus, parasite, or predator, then that claim broadens the scope of claim 71.

Claim 97 is objected to for the same reason. The claim could indicate (see the indefinite rejection below) that the target gene is located in a virus, parasite, or predator of an organism (plant). However, parent claim 93 indicates that the target gene is in the organism.

Claim 108 is also objected to for the same reason. Parent claim 102 does not encompass the mRNA being transcribed in a parasite or predator of a plant containing the cell.

It is noted that the elected species is plants. The elected invention is being examined to the extent that the methods involve introducing SRMs into plant cells or plants, and that the target gene is located in plant cells or plants.

Claim 77 attempts to limit the method of claim 60 limiting the SRM to comprise short sense and antisense molecules complementary to a sequence contained in a gene that encodes a gene product. However, parent claim 60 indicates that the sequences of the SRMs are complementary to the mRNA that encodes the gene product. Claim 60 does not encompass SRMs whose sequences are complementary to the gene encoding the gene product.

In claim 100: the term, "acid" should be inserted after "nucleic" in line 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 33, 35, 40-44, 75, 77, 78, and 93-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 33 and 40: the recitation, "silencing agent" renders the claim indefinite. The specification on page 8 states, "'Silencing agent' in this context may be one or more of an inducer, signal, or specificity determinant of gene silencing, particularly PTGS. Preferably this will be a SARM (as opposed to a SSRM)" (emphasis added). The term "may" is open language.

The recitation can therefore encompass other things. It is unclear what other things can be considered to be such agents. It is also unclear what is considered to be an inducer, signal, or specificity determinant.

In claims 35, 41, and 42: the recitation, "silencing agent comprises short RNA molecules" renders the claims indefinite. As indicated above, a silencing agent can be a SARM itself. However, it is unclear, for the reasons cited above, what kind of silencing agents can comprise short RNA molecules.

In claims 75: the recitation, "target gene is expressed by a virus, parasite or predator of an organism containing said target gene" renders the claim indefinite. It is unclear where the target gene is located. The recitation states that the gene is expressed by the virus parasite or predator, indicating that it is located in the virus, parasite, or predator. However, the claim also indicates that the organism (plants are the elected species) contains the target gene.

In claims 77, 100, and 109: the recitation, "said SRM comprises short sense and antisense molecules complementary to a sequence contained in a gene that encodes said gene product" renders the claim indefinite. It is unclear how the SRM can contain both sense and antisense molecules. The specification states, "The term 'SRMs' is used to describe the short RNA molecules described herein which are approximately 25 nucleotides in length. The size appears to be very characteristic, being estimated as approximately 25 nucleotides in all the cases tested (relative to the same molecular size markers when assessed by chromatography). However, it may be slightly more or less than this characteristic length (say plus or minus 1, 2, 3, 4 or 5 nucleotides) and where the term '25 nt RNA' is used herein, it will be understood by those skilled in the art that the comments would apply equally in the event that the SRMs do not have

this precise length" (page 4). The discussion of SRMs on page 4 also distinguishes SRMs that consist of antisense sequences from those that consist of sense sequences (lines 20-25). It is therefore unclear how the same SRM can have both antisense and sense sequences. It is also unclear how sense and antisense sequences can both be complementary to the same sequence in the gene.

In claim 93: the recitation, "characterized as" in line 5 renders the claim indefinite. It is unclear how this recitation defines the SRM. Does the SRM consist of, or comprise, 25 nucleotides plus or minus, 1, 2, 3, 4, or 5 nucleotides?

In claim 97: the recitation, "said target gene is comprised in a virus, parasite or predator affects an organism containing said gene" renders the claim indefinite. The meaning of this recitation is unclear.

In claim 102: the recitation, "equivalent cell" in line 6 renders the claim indefinite. It is unclear what is to be considered an "equivalent". The metes and bounds of the claim are unclear.

Further in claim 102: the recitation, "said cell" in line 11 renders the claim indefinite. It is unclear which cell, the cell mentioned in line 2 or the equivalent cell in line 6, is being referred to.

In claims 104 and 105: the recitation, "said cell" renders the claims indefinite. It is unclear which cell, the cell mentioned in line 2 or the equivalent cell in line 6 of claim 102, is being referred to.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 33-44, 60-80, 83, and 93-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method when the nucleic acid sequence that is introduced into the cell to cause PTGS is double-stranded or if single-stranded, is not as small as 30 nucleotides, does not reasonably provide enablement for the claimed method with single-stranded SRMs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn towards a method of silencing a target gene in an organism (the elected species is plants) by post-transcriptional gene silencing (PTGS), comprising introducing into a plant a silencing agent which targets a targeted region of said target gene, wherein the silencing agent comprising short RNA molecules (SRMs) which are 25 nucleotides long plus or minus 1-5 nucleotides, and which are specific for the targeted region of the target gene, or wherein the SRMs are short anti-sense RNA molecules (SARMs) and/or short sense RNA molecules (SSRMs); or a method of inhibiting the translation of a gene product in a plant cell by PTGS, comprising introducing into said cell at least one SRM, wherein the SRM has a sequence complementary to an mRNA that encodes said gene product; or a method of introducing systemic PTGS of a target gene in a plant, comprising introduction of a SRM or a transcribable nucleic acid construct encoding a SRM wherein the SRM is characterized as 25 nucleotides in length, plus or minus 1-5 nucleotides and which have a nucleic acid sequence complementary to a portion of said target gene; or a method if inducing PTGS in a plant cell

comprising introduction of a selected nucleic acid sequence wherein said nucleic acid is selected based on a finding that it induces the production of short 20-30 nucleotide RNA molecules when introduced into an equivalent cell, wherein the nucleic acid is sufficiently complementary in sequence specificity to a mRNA otherwise present in said cell to interfere with the stability and translation of said mRNA.

The specification indicates that SRMs may be mediators of post-transcriptional gene silencing. SRMs are defined on page 4 as short RNA molecules 25 nucleotides in length, plus or minus 1-5 nucleotides (page 4, lines 4-14). The specification also indicates that, in performing the invention, it may be preferred to utilize SARMs rather than SSRMs, although it is to be understood that SSRMs can be used wherever SARMs are referenced (page 4, lines 20-25). This indicates that SRMs are single-stranded RNA molecules that are in sense or anti-sense orientation relative to their target sequence. The specification indicates that the invention includes methods for inducing PTGS of a target gene in an cell or organism, including plants, comprising the introduction of SARMs (page 10, lines 6-11; page 13, line 28 to page 14, line 29, for example). Working Example 1 teaches that 25 nucleotide long RNAs accumulated in transgenic plants, transformed with an ACO cDNA sequence operably linked to the CaMV 35S promoter, as a result of co-suppression of the cDNA and endogenous ACO gene. The 25 nucleotide long RNAs were of sense and antisense polarity of sequences found in the ACO coding sequence. Example 1 also teaches that sense and antisense 25 nucleotide long RNAs, corresponding to the GUS coding sequence, were produced in transgenic tobacco plants that displayed PTGS of a GUS transgene.

However, the specification does not enable the silencing of a target gene or inhibition of translation of a gene product by PTGS in a cell, by introducing into the cell and expressing single-stranded nucleic acid molecules that are 20-30 nucleotides long. There are numerous examples in the prior art of inhibiting a target gene by expressing a coding sequence, or a fragment thereof, of that gene in anti-sense orientation, and of co-suppressing a target gene by introducing the coding sequence, or a fragment thereof, of the gene in sense orientation. However, there appears to be a minimum size limit to single-stranded nucleic acids that can trigger PTGS of its target sequence. Klahre et al. (PNAS, 2002, Vol. 99, pages 11981-11986) have shown that 21-nt sense and 22-nt antisense single-stranded nucleic acid molecules could not induce PTGS of their target sequence. Of nucleic acid molecules that small, only double-stranded molecules (siRNAs), which also contain 2- and 3-nt 3' overhangs, could cause silencing (pages 11982-11983). Further, the silencing was highly sequence specific. siRNAs that had mismatches with the target sequence could not trigger silencing (page 11984). While the instant specification teaches that 25 nucleotide SRMs are produced during PTGS in plants, it does not show that such single-stranded nucleic acid molecules can initiate PTGS of the target gene by introducing and expressing them in a plant cell. In the absense of further guidance, undue experimentation would be required by one skilled in the art to cause PTGS of a target gene using single-stranded SRMs.

Further, regarding claim 76: the claim indicates that the target gene to be suppressed is involved in parasite resistance. The specification does not teach how one skilled in the art would use such a plant produced by the method, since it would be more susceptible to parasites. See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches

that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. Given the breadth of the claims, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention. Given the breadth of the claim encompassing the introduction of nucleic acid sequences that are as small as 30 nucleotides and single-stranded, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9. Claims 33-44, 60-80, 83, and 93-110 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 33-44, 60-80, 83, and 93-110 are of copending Application No. 11/013,469. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The recited claims of both applications are identical.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 33, 35, 37-44 are rejected under 35 U.S.C. 102(b) as anticipated by Hamilton et al. (Plant J., 1998, Vol. 15, pages 737-746).

The claims are broadly drawn towards a method of silencing a target gene in an organism (the elected species is plants) by post-transcriptional gene silencing (PTGS), comprising introducing into a plant a silencing agent which targets a targeted region of said target gene, wherein the silencing agent comprising short RNA molecules (SRMs) which are 25 nucleotides long plus or minus 1-5 nucleotides, and which are specific for the targeted region of the target gene, or wherein the SRMs are short anti-sense RNA molecules (SARMs) and/or short sense RNA molecules (SSRMs).

Hamilton et al. teach transgenic tomato plants transformed with a tomato ACO1 cDNA operably linked to a promoter, wherein ACO1 expression from the transgene and the homologous endogenous gene was subjected to PTGS (pages 738-740). The ACO1 transgene can be considered to be a silencing agent of the endogenous ACO1, as the instant specification does not precisely define "silencing agent" (see the indefinite rejection above). The tomato ACO1 cDNA corresponds to the endogenous ACO1 gene in the host tomato plant, and so the mRNA transcribed from the cDNA inherently comprises 25 nucleotides plus or minus 1-5 nucleotides that are specific for the endogenous ACO1 mRNA transcribed from the endogenous

gene. One of the constructs also comprised 70 bases of the 5' untranslated region of the ACO1 cDNA in reverse orientation (page 738).

11. Claims 33-44, 60-80, 83, and 93-110 are rejected and non-elected claims 45-59, 81, 82, and 84-92 are withdrawn from consideration.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Jones, can be reached at 571-272-0745. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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October 17, 2005

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